



# Changes in oral anticoagulation for elective cardioversion: results from a European cardioversion registry

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## Aims

In patients with atrial fibrillation (AF) pharmacological or electrical cardioversion may be performed to restore sinus rhythm. The procedure is associated with an increased risk of thromboembolic events, which can be significantly reduced by adequate anticoagulation (OAC). Our aim was to create a partly prospective, partly retrospective cardioversion registry, particularly focusing on OAC strategies in different European countries, and on emerging choice of OAC over time.

## Methods

From September 2014 to October 2015, cardioversions due to AF performed in six European city hospitals in five European countries (Hungary: Budapest-1 and -2; Italy: Bari and Pisa; France: Amiens; Spain: Madrid; and Lithuania: Kaunas) were recorded in the registry.

## Results

A total of 1101 patients (retrospective/prospective: 679/422, male/female: 742/359, mean age: 67.3 years  $\pm$  11.2) were registered. Most of the cardioversions were electrical (97%). Oral anticoagulants were administered in 87% of the patient, the usage of non-VKA oral anticoagulants (NOACs) vs Vitamin K antagonists (VKA) was 31.5% vs 68.5%, respectively. Seventy seven percent of the patients were given oral anticoagulants more than 3 weeks prior to the procedure, and 86% more than 4 weeks after the procedure. When using VKA, international normalized ratio (INR) at cardioversion was above 2.0 in 76% of the cases. A decline in VKA usage ( $P=0.033$ ) in elective cardioversion over approximately 1 year was observed. During the observation period, there was an increase in apixaban ( $P<0.001$ ), a slight increase in rivaroxaban ( $P=0.028$ ) and no changes in dabigatran ( $P=0.34$ ) usage for elective cardioversion. There were differences in use of OAC between the countries: Spain used most VKA (89%), while France used least VKA (39%,  $P<0.001$ ).

## Conclusion

According to current AF guidelines, NOACs are adequate alternatives to VKA for thromboembolic prevention in AF patients undergoing elective cardioversion. Our results indicate that NOAC use is increasing and there is a significant decrease in VKA use.

## Keywords

Atrial fibrillation • Cardioversion • Registry • Anticoagulation • NOACs

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## Introduction

Atrial fibrillation or flutter (AF) is the most common type of sustained cardiac arrhythmia. To restore sinus rhythm one option is to perform a cardioversion. There are two types of cardioversions: pharmacological and electrical. The procedure is associated with a risk of thromboembolic events, most commonly ischaemic stroke.<sup>1</sup> Adequate anticoagulation can significantly reduce the incidence of thromboembolic complications. According to current AF guidelines (ESC 2016<sup>2</sup> and AHA/ACC 2014<sup>3</sup>) adequate oral anticoagulation (OAC) is recommended for at least 3 weeks prior to and for 4 weeks after cardioversion in patients with AF of  $\geq 48$  h or unknown duration. As an alternative to OAC, transoesophageal echocardiography can be performed before cardioversion to rule out left atrial thrombus.

Vitamin K antagonists (VKA) can prevent thromboembolic episodes during cardioversion.<sup>4</sup> A great amount of clinical experience is available on VKA,<sup>5</sup> but there are some limitations to their usage, such as the requirement of continuous laboratory monitoring and the numerous drug and food interactions. Since the advent of non-VKA oral anticoagulants (NOACs) there are now several alternatives used for prevention of stroke in patients with AF.<sup>6–12</sup> The NOACs comprise dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban and edoxaban, which are direct Xa factor antagonists.

With regards to cardioversion, X-VERT was the first prospective randomized trial to show that rivaroxaban can prevent thromboembolic complications as effectively as VKA in patients undergoing cardioversion.<sup>13</sup> Also the recently published ENSURE-AF<sup>14</sup> trial and the *post hoc* analyses of the RE-LY<sup>15</sup> and ARISTOTLE<sup>16</sup> trials proved that edoxaban, dabigatran, and apixaban can be safely used as well. In addition, several single-centre trials and meta-analyses confirmed the low number of thromboembolic events and safe use of NOACs during cardioversion.<sup>17–20</sup>

## Aims

Our aim was to create a partly prospective and partly retrospective cardioversion registry, particularly focusing on OAC strategies in different European countries (Hungary, Italy, France, Spain, Lithuania), and on emerging choices over time for anticoagulants in this setting.

## Methods

### Design and patients

All patients in the study centres who underwent electrical or pharmacological cardioversion of AF or flutter were included in the registry. Patient records were collected in seven cardiology departments of six different European cities in five European countries, namely (i) Budapest—Hungary, (ii) Budapest—Hungary, (iii) Pisa—Italy, (iv) Bari—Italy, (v) Madrid—Spain, (vi) Amiens—France, and (vii) Kaunas—Lithuania.

Data were recorded between September 2014 and October 2015, in the 7 months prior to start date of the registry, and in the 6 months following the start date of the registry. The retrospective and prospective design was chosen in order to align the timing to the 12 months following the presentation of the X-VERT trial, in order to assess whether its publication would influence NOAC uptake in the cardioversion setting.

Data collection was performed in in-patient and out-patient cardiology departments. All cardioversions during electrophysiological procedures were excluded; also data from emergency departments were not collected. Cardioversions were performed according to local protocols. The study was approved by the ethics committee in participating centres/country. For all patients a case report form was completed, and subsequently databased. Cardiovascular endpoints were not assessed in this registry.

### Statistical methods

We used the Pearson chi-squared test to compare NOAC vs. VKA in *de novo* prescriptions prior to scheduled cardioversion (yes/no), duration of OAC before cardioversion (more/less than 3 weeks), and duration of OAC after cardioversion (more/less than 4 weeks). The Pearson chi-squared test was also used to compare Spain and France in use of anticoagulants (yes/no). To analyse changes in OAC usage over time, we used logistic regression with OAC (yes/no) as the outcome variable and the number of months since 1 January 2014 as explanatory variable. The plots of OAC usage over time were smoothed with 1-nearest-neighbour and 2-nearest-neighbour averaging. Stata 14 (StataCorp LP) and Matlab 2014 (Mathworks, Inc) were used to perform the statistical analyses.

## Results

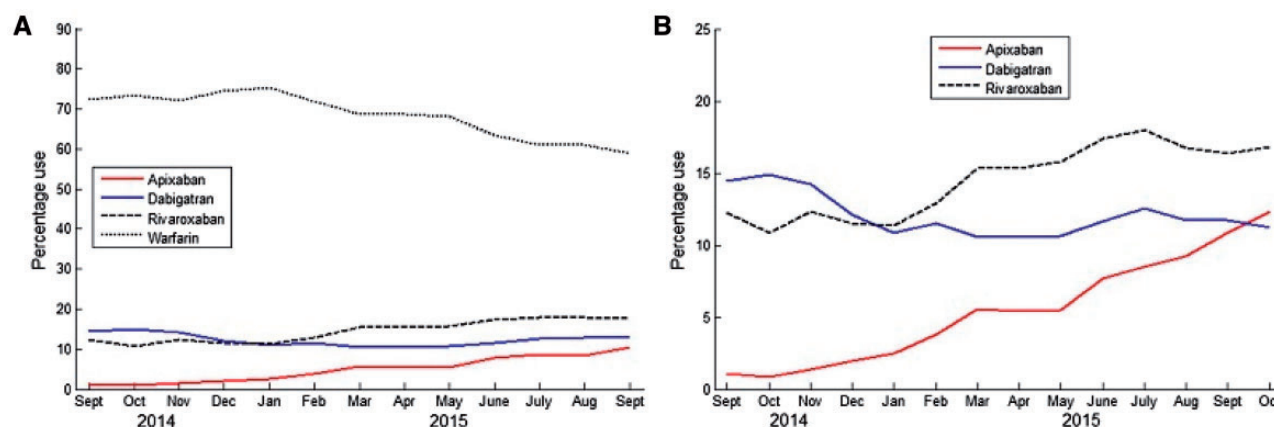
A total of 1101 patients (male/female: 742/359, mean age: 67.3 years  $\pm$  11.2) were included in the registry. Six hundred and seventy-nine retrospective and 422 prospective cases were collected. Most of the cardioversions were elective (1050 cases), acute cardioversions were done only 51 times, where acute procedure was defined as a cardioversion performed on a haemodynamically unstable patient. Nearly all cardioversions were electrical (97%), only 3% were pharmacological. 405 patients were recorded in Hungary, 200 in Italy, 193 in Lithuania, 186 in Spain, and 116 in France.

Oral anticoagulants were administered in 87% of the patients. The usage of NOACs vs. VKA was 31.5% vs. 68.5%, respectively. Thirteen percent of the subjects were cardioverted without oral anticoagulants, because of an AF duration of  $<48$  h in most cases (83.3%).

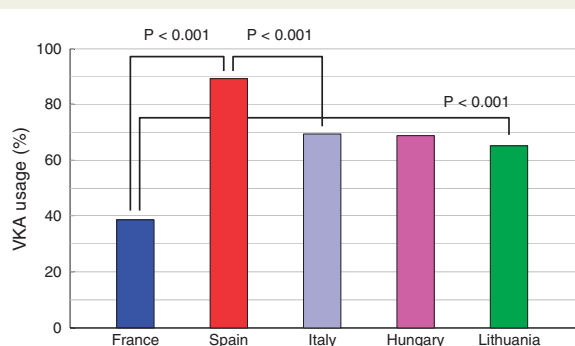
OAC prescription habits were also documented. No differences were found between NOACs and VKA in *de novo* prescriptions prior to scheduled cardioversions (NOAC: 20% vs. VKA: 19%;  $P=0.68$ ). Also we analysed previously anticoagulated and treatment-naïve patients, and there were no differences in the use of NOACs and VKA between the groups (previously prescribed: 30.2% NOACs vs. new treatment: 30.3% NOACs,  $P=0.99$ ).

Also there were no differences between the duration of OAC before cardioversion, i.e. most of the patients received 3 or more weeks of OAC in both the NOACs and the VKA groups (86% vs. 84%;  $P=0.51$ ). In 87% of the patients taking NOACs and in 84% of those taking VKA, the anticoagulants were given for more than 4 weeks after the procedure ( $P=0.14$ ). When using VKA, international normalized ratio (INR) at cardioversion was above 2.0 in 76% of the cases.

When examining OAC strategies over time a decline in VKA usage ( $P=0.033$ ) in elective cardioversion over approximately 1 year was observed (Figure 1A). During the observation period an increase in apixaban ( $P<0.001$ ), a slight increase in rivaroxaban ( $P=0.028$ ) and no changes in dabigatran ( $P=0.34$ ) usage for elective cardioversion was recorded (Figure 1B).



**Figure 1** (A) Changes in OAC usage over time. (B) Changes in NOAC usage over approximately 1 year (enlarged portion of Figure 1A).



**Figure 2** VKA usage in different European countries.

There were differences in use of anticoagulants between the countries: Spain used most VKA (89%), while France used least VKA (39%,  $P < 0.001$ ). There were no large differences in VKA usage between Italy, Hungary and Lithuania (Figure 2).

## Discussion

According to large randomized prospective clinical studies, NOACs were shown to be at least non-inferior to VKA in the prevention of stroke in patients with AF.<sup>6-9</sup> Further, NOACs have been shown to be safe alternatives to VKA during cardioversion.<sup>13-16</sup>

To examine anticoagulation strategies in different European countries our research group created a cardioversion registry of 1101 patients enrolled over approximately 1 year. According to our results only approximately 3/4 of the patients receiving VKA reached therapeutic INR levels during cardioversion, which is a concern given the predominantly elective and iatrogenic nature of cardioversion and

the known increased risk for thromboembolism. On the other hand, in our registry most patients received anticoagulation more than 3 weeks before and more than 4 weeks after cardioversion which is similar to the results of the European Heart Rhythm Association Survey.<sup>21</sup> No differences were observed between the NOACs and VKA groups in the duration of OAC. In the X-VERT<sup>13</sup> trial a significantly shorter time to cardioversion was observed in the rivaroxaban group as opposed to the VKA group. According to the ENSURE-AF<sup>14</sup> trial there was no difference in time to cardioversion between the edoxaban and warfarin group, which was explained by optimized warfarin dosing and enoxaparin bridging therapy. In our study, the exact duration from start of treatment to the cardioversion procedure was not registered. However, the relatively low number of subjects reaching therapeutic INRs may indirectly suggest that patients underwent a longer treatment period in the VKA group, and hence a reduced time to cardioversion in the NOAC group after the initial 3 weeks.

One of the conclusions of our registry is that despite several practical advantages of NOACs over VKAs, clinicians appear to hesitate to embrace their usage during cardioversions. According to a Norwegian registry in total 32 675 patients with AF 65.1% was given NOACs, but in our cardioversion registry the usage of NOACs was only 31.5%.<sup>22</sup> One of the reasons may be that compliance (persistence and adherence) is harder to monitor in NOACs than in VKAs, which is of extreme importance when performing cardioversion.

The slight increase in rivaroxaban usage over time might well be a reflection of the publication of the X-VERT trial in 2014, the first prospective trial to show the safety and efficacy of a NOAC during cardioversion when compared to warfarin. Dabigatran was the first choice in most of the countries in the first 4 months of our observational period, and it remained at a stable usage ratio. Apixaban was the least prescribed NOAC during the first few months, but a substantial increase throughout the observational period of one year was recorded. In a Danish registry between 2011 and 2015, a decreasing usage of VKA in general AF management was observed, and among

NOACs a rise of apixaban and a decrease of dabigatran was noticed.<sup>23</sup> Similarly, an expanding use of NOACs was reported in the GARFIELD-AF registry, and there were differences between countries similar to our results in the cardioversion population.<sup>24</sup> Differences of NOAC usage between countries depend predominantly on regulatory as well as economic factors.

The design of this registry purposely focused on the use of oral anticoagulants, however outcome data of stroke and systemic embolism and safety endpoints such as bleeding events would be of great additional value to this work. These will be subject for future research and will receive highest priority.

## Conclusions

Taken together, our study shows that most patients did receive oral anticoagulants during cardioversion. VKAs were used more often (2/3 vs. 1/3) than NOACs in this particular setting. However, our results show a significant decrease in VKA usage over time, while NOAC usage displays a gradual increase. As NOACs are more and more widely used in AF in general, further studies in the cardioversion setting will be needed to understand their optimal role in this aspect of AF patient management.

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